Differences in Membrane Properties in Simulated Cases of Demyelinating Neuropathies: Internodal Focal Demyelinations with Conduction Block

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Abstract. The aim of this study is to investigate the membrane properties (potentials and axonal excitability indices) in the case of myelin wrap reduction (96%) in one, two and three consecutive internodes along the length of human motor nerve fibre. The internodally focally demyelinated cases (termed as IFD1, IFD2 and IFD3, respectively, with one, two and three demyelinated internodes) are simulated using our previous double cable model of the fibre. The progressively greater increase of focal loss of myelin lamellae blocks the invasion of the intracellular potentials into the demyelinated zones. For all investigated cases, the radial decline of the extracellular potential amplitudes increases with the increase of the radial distance and demyelination, whereas the electrotonic potentials show a decrease in the slow part of the depolarizing and hyperpolarizing responses. The time constants are shorter and the rheobases higher for the IFD2 and IFD3 cases than for the normal case. In the recovery cycles, the same cases have less refractoriness, greater supernormality and less late subnormality than the normal case. The simulated membrane abnormalities can be observed *in vivo* in patients with demyelinating forms of Guillain-Barré syndrome. The study provides new information about the pathophysiology of acquired demyelinating neuropathies.

Key words: acquired demyelinating neuropathies, computational neuroscience, potentials, strength-duration properties, recovery cycles

1. Introduction

In demyelinated nerve fibres, the loss of the insulation provided by myelin characterizes a number of common neurological diseases. In some of these disorders such as Charcot-Marie-Tooth disease type 1A (CMT1A) [1, 2], the demyelination uniformly affects the nerve, whereas in other disorders such as Guillain-Barré syndrome (GBS) and multifocal motor neuropathy (MMN) the demyelination process affects the nerve focally. GBS is classified into acute inflammatory demyelinating polyneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) by pathological and electrodiagnostic criteria [3–5]. A critical diagnostic feature in the MMN is the demonstration of conduction block in multiple peripheral nerves on electrophysiological investigations [6, 7]. In the 1990s, the non-invasive

threshold tracking technique was developed to measure threshold electrotonus and several indices of axonal excitability, such as strength-duration time constants, rheobases and recovery cycles. These indices, which depend on the biophysical properties of the axonal membrane and myelin sheath, can now be measured in healthy subjects and patients with demyelinating neuropathies [8–12]. Recently, the method of mathematical modelling has also been applied as a promising tool for studying excitability properties in nerve disorders [13–17]. Our previous study [16], investigating membrane properties in simulated cases of CMT1A, shows that greater negative electrotonic responses, longer strength-duration time constants, and greater refractoriness and supernormality in the recovery cycles can be used as specific indicators of internodal systematic demyelinations (ISD). The uniformly reduced amplitudes, prolonged duration and slowed conduction velocities of the intracellular potentials are also characteristic of these abnormal cases. Furthermore, our previous study [17], investigating the membrane properties in simulated internodally focally demyelinated (IFD) cases without conduction block, shows that the changes in the excitability indices match those recorded *in vivo* in patients with Guillain-Barré syndrome. Both in patients and in the simulations, the changes are so slight that they are difficult or impossible to distinguish from normal values. As a continuation of the cited paper, the aim of the present study is to investigate again the abnormalities in the membrane properties for the same IFD types, but in the case of conduction block, since actually almost all symptoms in GBS patients are caused by conduction block. The results are again consistent with the interpretation that the morphological factors causing focal myelin wrap reduction could be responsible for the obtained abnormalities in the potentials and axonal excitability indices.

2. Methods

The electrogenesis of myelinated human motor nerve fibre can be studied successfully using the double cable model of the fibre [18–20]. The interested reader is referred to the first figure of [18] for an electric equivalent circuit representation of the human motor fibre. In the cited paper, Kirchhoff's current law is used to derive a system of partial differential equations for the electric equivalent circuit. This circuit is based on a complex extended double cable structure of nodal, paranodal and internodal segments with their corresponding ion (nodal and internodal) channels. The ion channel types and their maximal permeabilities are taken from the well-known two-component (node + internode) model of human motor axons [21]. However, that model ignores spatial gradients of potentials and currents within internodes and cannot propagate intracellular potentials. This means that the membrane parameters such as R_{ax} (axoplasmic resistance), R_{pa} (periaxonal resistance) and R_{pn} (paranodal seal resistance) are not incorporated. These new membrane parameters and their values involved in the double cable model have been thoroughly

discussed previously [18–20]. The model assumes a high-resistance myelin sheath and a leakage pathway to the internodal axolemma via the paranodal seal resistance and periaxonal space. The model fibre comprises 30 nodes of Ranvier and 29 internodes. Each internode is divided into 2 paranodal and 5 internodal segments. The same double cable model is used here to simulate focal demyelinations, which are defined as a reduction (96%) of the myelin lamellae in one (10th), two (9th and 10th) and three (8th, 9th and 10th), respectively, consecutive internodes along the fibre length. For this severe (96%) demyelination, the internodally focally demyelinated cases with one, two and three demyelinated internodes are termed as IFD1, IFD2 and IFD3, respectively. In the normal case, the fibre has $N = 150$ myelin lamellae. Its myelin sheath is characterized with C_{my} (myelin capacitance) 1.5 pF and R_{my} (myelin resistance) 250 M Ω . Each parameter value for a given spiral differs in arithmetic progression with N . The rule of the arithmetic increasing or decreasing of the value, however, depends on the type of the given parameter. For the investigated demyelinations, the myelin parameter values are $N = 6$, $C_{my} = 37.5$ pF, $R_{my} = 10$ M Ω . The demyelinations are associated with a corresponding loosening of the myelin lamellae away from the axolemma in the given internodal segments. The other membrane parameter values for the human motor fibre are the same as described earlier [18, 20], i.e. C_n (nodal capacitance) 1 pF, C_i (internodal axolemmal capacitance) 350 pF, R_{ax} (axoplasmic resistance) 8 M Ω , R_{pa} (periaxonal resistance) 300 M Ω , R_{pn} (paranodal seal resistance) 125 M Ω , V_r (nodal resting potential) -86.7 mV, V_{ra} (internodal axolemmal resting potential) -86 mV, I_{pump}^* (net outward current generated by electrogenic Na^+/K^+ pump) 0.1 nA; channel types and maximum permeabilities ($\text{cm}^3\text{s}^{-1} \times 10^{-9}$): node, Na (sodium) 9, K_f (fast potassium) 0.07, K_s (slow potassium) 0.26; internode, Na^* (sodium) 80, K_f^* (fast potassium) 27, K_s^* (slow potassium) 2, IR^* (inward rectifier) 0.008, L_k^* (leak) 0.0064; ion concentrations (mM): $[\text{Na}^+]_i$ 9, $[\text{Na}^+]_o$ 144.2, $[\text{K}^+]_i$ 155, $[\text{K}^+]_o$ 3. We would like to remind the reader that the channel types are also in accordance with the directly investigated ion channels in human axons [22, 23]. The resting potential (-86.7 mV) as an especially sensitive variable is derived from measurements on human ulnar nerve [21] and on human myelinated nerve fibres [23]. This value is more negative than those reported in rabbit (-80 mV, [24]) and rat (-80 mV, [25]; -78 mV, [26, 27]). All calculations are carried out for fibres with an axon diameter of $12.5 \mu\text{m}$. The lengths of node, paranode and nodal center to nodal center are $1.5 \mu\text{m}$, $200 \mu\text{m}$ and $1400 \mu\text{m}$, respectively. The temperature is 37°C . The normal myelin thickness of $2.4 \mu\text{m}$ gives an external fibre diameter of $17.3 \mu\text{m}$. In the IFD1, IFD2 and IFD3 cases both the myelin thickness and external diameter are reduced in the demyelinated zone. The myelin thickness is reduced by 96% in the demyelinated zones and the external fibre diameter of $17.3 \mu\text{m}$ is reduced to $12.7 \mu\text{m}$ in these severely demyelinated zones.

The 96% myelin reduction value is the final degree of focal demyelination for one internode after which conduction block is achieved. The 70% myelin reduction value involved in the previous papers [14–16] is close to the final degree of

systematic demyelination for achieving conduction block. These values allow different demyelination types (systematic and focal) to be compared.

Stimulation to produce intracellular potentials is simulated by adding a short (0.1 ms) rectangular current pulse to the center of the first node to correspond to the case of point fibre polarization. This case of intracellular point current application at the node closely approximates the effects of external point stimulation with a needle electrode and realizes a point fibre polarization. The intracellular potentials in the case of adaptation are simulated by adding a long-lasting suprathreshold depolarizing pulse. This case closely approximates the effects of external surface stimulation with a large electrode and realizes a periodic kind of uniform fibre polarization. The model-generated intracellular potentials, in the second case of fibre stimulation, are then used as input to a line source model [28], that allows the calculation of the corresponding extracellular potentials at various radial distances in the surrounding volume conductor. The electrotonic potentials are simulated by adding a 100 ms subthreshold current to the center of each internodal segment and the case of periodic kind of uniform fibre polarization is also realized. The periodic kind of uniform polarization is first simulated in the human motor electrotonus model [19], since the *in vivo* situation for recording threshold electrotonus in man, where current is applied to the peripheral nerve via its high-resistance sheath and a 1 cm diameter surface electrode [21], is thought to correspond more closely to periodic kind of uniform polarization than point fibre polarization. The potentials are calculated for hyperpolarizing and depolarizing currents, which correspond to 0.4 times the threshold for a 1 ms current pulse.

The indices of the axonal excitability (such as strength-duration curves, charge-duration curves, strength-duration time constants, rheobasic currents and recovery cycles) obtained from single or pairs of threshold stimuli are investigated in the case of adaptation. The strength-duration time constants and rheobasic currents are calculated by the method, which is described earlier [13–17] and, in brief, the threshold stimulus duration is increased in 0.025 ms steps from 0.025 ms to 1 ms, to obtain the strength-duration curves. A polynomial function of degree 2 (transfer standard parabola), which relates threshold charge (Q) to stimulus duration (t), provides an accurate fit of the data: $Q = a_2[t^2 + (a_1/a_2) \cdot t + a_0/a_2]$, where a_0 , a_1 , a_2 are the polynomial coefficients. The strength-duration time constant is defined as the absolute value of the smallest square root of the function (i.e. only one of both direct intercepts of the regression curve on the duration axis has a biophysical sense and only this direct intercept is shown on the given figures below). The rheobase is defined as the final decreased threshold value, after which potential generation is not obtained with the increase of the stimulus duration. When two equal pulses are used in pairs, the response of the second (testing) pulse in the refractory period may be greater or less than the response of the first (conditioning) pulse, depending on the conditioning-test intervals. To obtain the time course of recovery of the axonal excitability following a single threshold stimulus (the recovery cycle), test stimuli of 1.0 ms duration are delivered at conditioning-test intervals of 2–100 ms after a

threshold conditioning stimulus of 1.0 ms duration. The recovery cycles depend on the regenerative depolarization caused by the first (conditioning) afterpotentials and can be explained by the delay-dependent second (testing) potentials. During the absolute refractory period when the inactivation of Na^+ channels is low and the activation of K^+ channels is high, the threshold potential (V_t) and the corresponding threshold current for the testing pulse are increased due to the more expressed increase of the critical membrane potential (E_c). [$(V_t = E_c - E_r)$; E_r is resting membrane potential]. By increasing the conditioning-test interval, E_c is decreased and as the membrane potential remains above E_r , the threshold potential becomes lower than that of the initial one. The result is the change from subnormality to supernormality of the membrane excitability.

The double cable model used has some limitations. First, the persistent Na^+ channels previously demonstrated in the nodes of human myelinated axons are not involved. According to [29] these channels can be excited by hyperpolarizing pulses and can affect the strength-duration time constants. As mentioned above, the strength-duration time constants are calculated here only in the case of depolarizing current application. Moreover, in the literature, there is no evidence that focal demyelinations could affect the distribution of these nodal channels. Consequently, the ignored persistent Na channels could not have an effect on the obtained results in the presented investigations. Secondly, the relatively complicated geometry of the myelin attachment region of the paranode is simulated with a paranodal seal resistance which joins each internode to the adjacent nodes of Ranvier. This simulation gives possibility for the accommodative responses to polarizing currents (i.e. electrotonic potentials) as well as the excitability properties in the case of adaptation to be investigated. The papers with complicated geometry of paranodal region [30, 31] cannot simulate and do not investigate the processes of accommodation and adaptation which are the basis of our investigations. Nevertheless these limitations, our double cable model still remains the only one in literature describing the membrane properties of normal and abnormal human myelinated nerve fibres. The findings may not necessarily be identical to those in human demyelinating neuropathies, which can be associated with additional factors such as activation of cytokines, complements or other inflammatory substances, resulting in dysfunction of ion channels, and macrophage invasion or nerve edema/fibrosis leading to structural changes. However, the simulated results [13–17] indicate that this model is a rather promising tool in studying the prominent features in neuropathies and neuronopathies which up till now have not been sufficiently well understood.

3. Results

A comparison between the intracellular and electrotonic potentials for the IFD1, IFD2 and IFD3 cases is presented for the human motor nerve fibres (Figure 1). The temporal intracellular potentials (Figure 1A) are at each node, from the 7th

Figure 1. Comparison between the intracellular (A) and electrotonic (B) potentials of human motor fibres in the IFD1, IFD2 and IFD3 (solid lines) cases, respectively, as the electrotonic potentials are compared with the normal case (dotted lines). The intracellular potentials in response to 0.1 ms threshold current pulses are presented at each node from the 7th to the 14th. The electrotonic potentials in response to 100 ms depolarizing and hyperpolarizing current pulses ($\pm 40\%$ of threshold) are also presented at each node from the 7th to the 14th.

to the 14th. In the IFD1 case, the conduction proceeds into, through and beyond the demyelinated zone. Although the rate of rise of the potential at the 7th, 8th, 9th and 10th nodes is gradually reduced, the potential recovers in the subsequent nodes. (The normal case with uniform amplitudes and velocities of the potentials along the fibre length is not given in Figure 1A). Moreover, in the regions distal to the demyelinated zone, for example, at the 14th node, the conduction occurs at its normal velocity and the potential amplitude achieves its normal value. The progressively greater increase of focal loss of myelin lamellae blocks the invasion of the potentials into the demyelinated zone for the IFD2 and IFD3 cases. In contrast, the IFD1 case is the final degree of internodal focal demyelination for an internodal segment, after which conduction block is achieved. Thus, with the increase of the demyelinated zone, conduction failure occurs more rapidly. The electrotonic potentials for the normal, IFD1, IFD2 and IFD3 cases are also compared (Figure 1B). The temporal distributions of the electrotonic potentials during and after 100 ms depolarizing and hyperpolarizing currents ($\pm 40\%$ of threshold) are again shown at each node, from the 7th to the 14th. However, for the normal case, each node behaves identically, and an overlap of the potentials at the nodes is obtained. When the normal case is compared with the IFD1, IFD2 and IFD3 cases, the obtained differences are the smaller slow positive and negative phases to the polarizing currents. The depolarizing and hyperpolarizing electrotonic potentials are similar, with the biggest drop to a minimum amplitude in the 10th node and with the largest increase to a maximum amplitude in the 7th and 14th nodes.

Figure 2 illustrates the temporal distributions of the intracellular potentials (V) and their corresponding extracellular potentials (P), in the normal, IFD1, IFD2 and IFD3 cases of the human motor fibres. For all cases, the potentials are again shown at each node, from the 7th to the 14th. However, for the normal case, each node behaves identically, and an overlap of the potentials at the nodes is obtained. The extracellular potential amplitudes depend on the radial distance of the field point. Close to the fibre membrane ($r = 0.05$ mm), the extracellular potentials have a two-phase shape, while further in the volume conductor ($r = 1.0$ mm), the potentials have the usual three-phase shape. At large radial distances ($r \geq 5$ mm), the potentials become the same in shape. Lengthening the demyelinated zone causes a more rapid decrease of the peak-to-peak amplitude of the potentials, as illustrated more explicitly in Figure 3. In this figure, the extracellular potential time courses for radial distance $r = 1$ mm are repeated from Figure 2. The potentials are plotted for the same eight consecutive nodes from the 7th to the 14th as shown in the first row, except in the second, third, fourth and fifth rows where the potentials are shown at only the 7th, 8th, 9th and 10th nodes, respectively. With the increase of the demyelinated zone from the IFD1 to the IFD3 cases, the peak-to-peak amplitude of the potentials gradually decreases. However, in the regions distal to the demyelinated zone the potentials retain their normal shapes.

Figure 2. In the case of adaptation, the temporal intracellular potentials (V) and their corresponding extracellular potentials (P) in the normal and three IFD cases are presented for human motor fibres. The intracellular potentials are simulated by adding long-lasting depolarizing pulses, which correspond to 1.1 times the threshold for a 1 ms current pulse. The potentials are shown at each node from the 7th to the 14th, respectively. The extracellular potentials are given for three radial distances ($r = 0.05, 1.0$ and 5.0 mm).

The strength-duration and charge-duration curves for the normal, IFD1, IFD2 and IFD3 cases are presented in Figure 4 (first row). To provide a better illustration of the strength-duration time constants and rheobasic currents, histograms are also shown (Figure 4, second row). The strength-duration time constant and rheobase for the normal human motor nerve fibre are 0.291 ms and 0.388 nA, respectively. The strength-duration and charge-duration curves for the IFD1 case are near-normal. With the increase of the demyelinated zone, the threshold currents are higher in the IFD2 and IFD3 cases than in the normal case. Moreover, the strength-duration time constants are shorter for these cases than for the normal case. The time constants decrease, whereas the rheobasic currents increase, with the increase of the demyelinated zone. There is an inverse relationship between the strength-duration time constant and rheobases of the normal motor axon, and this is the same for the simulated IFD cases. The strength-duration time constants are 0.290, 0.256, 0.250 ms and the rheobases are 0.391, 0.398, 0.431 nA for the IFD1, IFD2 and IFD3 cases, respectively.

The excitability changes in the normal, IFD1, IFD2 and IFD3 cases during 100 ms recovery cycles of the fibres are illustrated in Figure 5. The recovery cycles

Figure 3. The extracellular potentials (P) in the normal, IFD1, IFD2 and IFD3 cases are repeated for the radial distance $r = 1.0$ mm. The superpositions of potentials are shown for eight consecutive nodes from the 7th to the 14th as shown in the first row, while in the second, third, fourth and fifth rows potentials shown are at the 7th, 8th, 9th and 10th nodes, respectively. *indicates the demyelinated internodes between the given nodes.

show that these changes in the normal and more severe IFD2, IFD3 cases are similar, however, in the abnormal axons they are bigger. The axonal types are initially unexcitable, then excitable with a raised threshold, and after about 2.3–2.5 ms they are superexcitable. In the unexcitable case, the axons are absolutely refractory, during which they cannot generate a second potential no matter how strong the testing depolarizing pulses are. The axons are then relatively refractory, during which a stronger than conditioning stimulus is required to generate second potential. In the superexcitable case, the testing stimulus necessary to generate second potential is less than the conditioning stimulus. The superexcitability is usually followed by a late subexcitability. The abnormal IFD2 and IFD3 axons have slightly less refractoriness, greater supernormality and less late subnormality than those for the normal axon. Moreover, their relatively refractory periods are shorter. The recovery cycle is atypical for the IFD1 case. In this case, the axon has greater refractoriness and longer relatively refractory period than the normal axon. The duration of each recovery period is different and depends on the degree of the demyelinated zone.

Figure 4. Comparison between the strength-duration curves, charge-duration curves, strength-duration time constants and rheobasic currents in the normal and three IFD cases of human motor fibres.

According to [8], the most appropriate electrotonic parameters to reflect demyelination at the stimulated site (i.e. outside the region of conduction block) are taken as the early and late depolarizing and hyperpolarizing responses [TEd (10–20 ms) (%); TEd (90–100 ms) (%); TEh (10–20 ms) (%) and TEh (90–100 ms) (%) after the start of polarizing currents]. These parameters measure the so-called early and late “fanning out” of the threshold electrotonus responses and depend on the applied polarizing currents and demyelinating factors. Analogous early and late electrotonic parameters [TEd (10–20 ms) (mV); TEd (90–100 ms) (mV); TEh (10–20 ms) (mV) and TEh (90–100 ms) (mV) after the start of polarizing currents] are also used here for the investigated electrotonic potentials. The values of these

Figure 5. Comparison between the recovery cycles in the normal, IFD1, IFD2 and IFD3 cases of human motor nerve fibres. For all investigated cases the y-axis is defined as $100 \times (I_{\text{test}} - I_{\text{cond}})/I_{\text{cond}}$ (%), where I_{test} (nA) and I_{cond} (nA) are the threshold currents of the testing and conditioning pulses, respectively.

parameters at each node (from the 1st to the 30th) give the spatial distribution of the membrane potential along the fibre length (Figure 6). The distributions are plotted only for the most severe IFD3 case and are compared with those of the normal case. The results show that at the early (mean 15 ms) and late (mean 95 ms) moments after the start of the polarizing currents, the abnormal “fanning in” of the electrotonic responses in the demyelinated location and its vicinities in turn leads to a compensatory “fanning out” of these responses outside this demyelinated zone. For the same moments, the spatial distributions of the membrane potential for the normal case are unchanged along the fibre length and are shown as straight lines.

4. Discussion

The present study shows a number of differences in the potentials (intracellular, extracellular, electrotonic) and excitability properties (strength-duration curves, charge-duration curves, strength-duration time constants, rheobases, recovery cycles) between the simulated normal and internodally focally demyelinated fibres in the cases of severe (96%) demyelinations.

Figure 6. Comparison between the early (15 ms) and late (95 ms) spatial distributions of the membrane potentials along the fibre in response to polarizing currents ($\pm 40\%$ of threshold) for the IFD3 (solid lines) and normal (dotted lines) cases. The dashed lines indicate the resting potential, whereas the short lines indicate the location of the demyelination.

In the IFD1 case without conduction block, an expected result is the gradually reduced amplitude, prolonged duration and slowed conduction velocity of the intracellular potentials passing through and beyond the demyelinated zone. The previously described kinetics of the ionic currents defining the intracellular potentials [32] shows that the simultaneous decrease of myelin resistance and increase of myelin capacitance in the demyelinated zone result in an increase of the external membrane current. (In the paranodal and internodal segments, the external membrane current is equal to the transmyelin current). The given explanation for the reduced conduction obtained is an increase in the transmyelin current generation and the limitation for the externally recorded nodal current to pass longitudinally via the paranodal seal resistance to the periaxonal space. In the more severe IFD2 and IFD3 cases, the progressively greater increase of focal loss of myelin lamellae blocks the invasion of the intracellular potentials into the demyelinated zones. The electrotonic potentials allow the accommodative responses to polarizing currents to be documented. The previously described kinetics of the ionic currents defining the normal electrotonic potentials [19] shows that the slow components of electrotonic, transaxonal and transmyelin potentials depend on the activation of the channel types in the nodal or internodal axolemma, whereas the fast components of the potentials are determined mainly by the passive cable responses, i.e. by the capacitances and resistances of the corresponding different segments along the fibre length. In the cited paper, it is shown that for the hyperpolarizing current pulses, the contribution of the activating inward rectifier (IR) channels dominates in the total ionic currents. For the depolarizing current pulses, the contribution of the activating potassium

(K^+) channels dominates in the total ionic currents. Furthermore, the depolarizing electrotonus is determined mainly by the activation of the slow potassium (K_s^+) channels and the other channels as sodium (Na^+) and fast potassium (K_f^+) have minor contribution to its generation. Our results show, that there is a slightly decrease in the accommodated responses to subthreshold depolarizing and hyperpolarizing currents in the IFD1 case. This suggests that, for the axon studied, the behaviour of internodal accommodative conductances is slightly affected by the demyelinating pathology. The same results have been obtained for AIDP patients which tend to have the smaller slow phase of threshold change to polarizing currents than normal subjects [10]. This study of demyelinating forms of GBS without conduction block fails to reveal consistent abnormalities in threshold electrotonus. Our results confirm that demyelinations not sufficient to develop conduction block do not significantly affect electrotonic potentials. The same is valid for the extracellular potentials. The present study shows that the transition from conduction slowing to conduction block leads to amplification of the degree of the potential changes, as the direction of these changes is kept the same. The electrotonic potentials in the IFD2 and IFD3 cases show a bigger decrease in the slow part of polarizing responses than those in the IFD1 case. For the same two cases, the axonal depolarization leads to a bigger reduction of the extracellular potential amplitudes in the demyelinated zone than those in the IFD1 case (Figure 3). The obtained potential abnormalities are consistent with a depolarizing block in the investigated demyelinated fibres. The spatial distributions of the membrane potentials along the fibre length to the polarizing currents (Figure 6) consistently confirm heterogeneity of the conduction blocks in the focally demyelinated fibres. This result indirectly suggests that, in a case of extracellular nerve stimulation caused by polarizing direct currents (DCs), the abnormalities in the compound muscle action potentials (CMAPs) at the site of conduction block may arise from depolarization or hyperpolarization. The anodal DCs should block motor conduction (depolarizing block) by eliciting membrane hyperpolarization. By reversing membrane depolarization at the site of the depolarizing block, anodal DCs should improve motor conduction. Vice versa, the hyperpolarizing block should worsen during hyperpolarizing anodal DSc. Such pathophysiological heterogeneity of conduction blocks discussed here is also observed in [7] for the MMN with conduction block. According to our unpublished data, MMN with conduction block could be regarded as based on the paranodal (or simultaneously on the paranodal internodal) focal demyelinations rather than as based on the internodal focal demyelinations. The results indicate that the changes in the membrane properties are bigger in the paranodally (or in the paranodally internodally) than in the internodally focally demyelinated fibres. This could also be confirmed by comparing the differences in the membrane properties between patients with demyelinating GBS [10] and MMN with conduction block [8].

The current study also shows that the indices of the axonal excitability, such as strength-duration and charge-duration curves, strength-duration time constants

and rheobases are near-normal in the investigated IFD1 case. The results show again that the transition from conduction slowing to conduction block leads to amplification of the degree of the excitability property changes, as the direction of these changes is kept the same. Only the IFD1 case (Figure 5) provides an exception. This demyelinated case just before conduction block is a critical level for the axonal refractoriness and relative refractory period. Such atypical recovery cycles have been recorded from [9] in AMAN patients.

Moreover, all obtained abnormalities in the potentials and axonal excitability properties are quite different from those of our previous reports [14–16], in which the model-simulated demyelinations (internodal, paranodal and paranodal internodal) without conduction block are systematic, not focal. These studies show that different systematic demyelinations define different demyelinating neuropathies such as CMT1A and chronic inflammatory demyelinating polyneuropathy (CIDP). A comparison between the present and cited reports confirms that the changes in the membrane properties even in the case of mild systematic demyelinations are abnormally greater than those in the case of severe focal demyelinations.

In conclusion, we simulate here for the first time abnormalities in the potentials and excitability indices, which can be used as specific indicators of severe internodal focal demyelinations of human motor nerve fibres. The changes in the excitability indices obtained in these simulations match those recorded *in vivo* in patients. Both in patients and in the simulations for the demyelinated case without conduction block, the changes in the electrotonic potentials, strength-duration time constants and rheobases are so slight that they are difficult or impossible to distinguish from normal values. However, the abnormal potentials and excitability indices in the demyelinated cases with conduction block are quite different from those in systematic (internodal, paranodal and paranodal internodal) demyelinations and can provide new information about the pathophysiology of acquired demyelinating neuropathies. The present and our previous studies show that the electrogenesis of demyelinating neuropathies such as CMT1A, CIDP, MMN and GBS is different.

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